had evidently been produced by the stones in the duct; the stones passing through into it, and finally the cyst closing behind them. It was a cyst of long formation, as no digestive ferments were found in it. The early jaundice was produced either by a preliminary swelling in the head of the pancreas, or, as the common duct passed directly through it; the passing of a pancreatic stone into the ampulla of Vater; or thirdly, by a biliary stone in the common duct, which had made its exit into the intestine. This last supposition is quite improbable, as there were no other stones in the gall bladder, or evidence of any having passed through its duct either in the history or autopsy findings.

The microscopical report, for which I am indebted to Dr. Mary Halton, pathologist of St. Luke's Hospital, shows an advanced stage of interlobular pancreatitis, with the Islands of Langerhans still well preserved, verifying Opie's observations that in this type the appearance of sugar in the urine occurs only at the very last stages of the disease.

CHEMICAL PATHOLOGY OF PANCREATIC DISEASE, WITH REFERENCE TO DIAGNOSIS.*

By PHILIP KING BROWN, M. D.

THE IMPORTANCE of the pancreas in the digestive process is so great that it seems strange that we should know so little of its pathological disturbances during life, and that our means of diagnosis of slight disturbances should be so limited. The attention which the organ and its functions has attracted in the last decade, has been productive of a number of extremely significant points. It is probable that there will be constantly new light thrown upon the function of the organ, and the end result of its activity, as found in the excretions, will enable us to determine the condition of the organ more accurately than at present. We are chiefly interested now in determining such conditions of the pancreas as result from tumors, cysts, calculi, and the inflammatory or degenerative processes due so frequently to primary disturbances in the gall bladder and occulsion of the common duct, and to passage of bile and infectious material into the pancreatic duct. I shall not concern myself with giving you the symptoms of these various conditions, but desire to call attention to such means as we have at hand of determining the activity of the gland, and of drawing conclusions in regard to its condition by examination of the excretions, by blood examination and by therapeutic measures. For it is certain that the functional activity of the gland can be definitely influenced by certain chemical stimuli, as for instance, the administration of hydrochloric acid, the extracts of pancreas itself, and by the administration of fat foods, and definite inferences may be drawn by the results obtained through these measures.

What concern us chiefly are the alterations in blood, urine and feces, and what may be learned from examination of the contents of cysts of the organ or fistulous discharges. In regard to the blood examination it is clear from the cases reported from the Massachusetts General Hospital, and by Opie in the Johns Hopkins *Bulletin,* January, 1901, that hemorrhagic pancreatitis causes a distinct leukocytosis. The relation of the leukocyte increase to the disturbance of the pancreas may be of little diagnostic value, because local peritonitis in the omental bursa will cause the same leukocytosis and a very strikingly similar pain, as will also perforating ulcer of the stomach, particularly of the posterior wall. Suppurative cholecystitis occurring without jaundice or tumor may complicate the diagnosis somewhat. Cysts and tumors of the pancreas are not apt to make quantitative blood changes, except in the anemia which may result, and except there be actual encroachment upon fundamental parts of the pancreas, either directly or by pressure, when we have the most significant clinical change, the appearance of glycosuria, of which I shall speak more fully later. With the occurrence of glycosuria, and of particular value in the diagnosis of the extreme conditions resulting from it, notably the diabetic coma, the methods of examination of the blood proposed by Williamson and Bremer are of extreme importance. These methods consist in utilizing the difference in the affinity to analine dyes of diabetic and nondiabetic blood. It has been pretty definitely settled that the reaction resulting from the addition of a weak alkaline solution of methylene-blue to the blood, noted by Williamson of Manchester, depends upon the presence of an increased quantity of sugar. Hyperglycemic blood decolorizes the solution on boiling, while normal blood does not. Bremer's test, also proposed as a method of determining hyperglycemia, has not been shown of definite value, because of the probability of its reacting to other substances than sugar. Bremer's method consists of staining a thick spread blood film heated to 140° C. with a 1 per cent aqueous solution of congo-red. Normal blood looks yellow to the eye, whereas diabetic blood looks greenish-brown. The reactions have been studied carefully by Futcher of Johns Hopkins, who arrives at the conclusion that they "are interesting but of no great diagnostic importance." Bremer's claim that the reaction persisted after the sugar disappeared from the urine was not substantiated. This was also

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true, in one case at least, of Williamson's test, but no reaction at all occurred in another, although over 200 gms. of sugar were eliminated by the patient that day.

The urine in diseases of the pancreas is an index to us of the functional activity of the gland, not alone in its relation to the burning of sugar in the body, but equally in its relation to the splitting of fats. Langerhans has shown that the disseminated fat necrosis accompanying acute pancreatitis, and certain other conditions of the organ, is due to a fat-splitting ferment, and Flexner has shown the presence of this ferment in the necrotic areas. It remained for Opie, following the same line of thought, to trace the elimination of this fat-splitting ferment, and in May, 1902, he reports a case in which it was found present in the urine of a fatal case of diabetes from acute pancreatitis. The elimination of the fat splitting ferment by the urine is taken as evidence of its occurrence in this disease in the circulation. The method used to determine its presence was proposed by Castle and Loevenhart in the *American Chemical Journal,* Vol. 24, No. 6. Ethylbutyrate, when acted upon by the ferment, is decomposed with the formation of butyric acid, whose presence is determined in the urine previously neutralized with potassium hydroxide by the addition of litmus solution. The control test is conducted by boiling the urine in order to destroy the ferment. Both specimens are subjected to a temperature of 37° C. for 24 hours.

An increase in *indican* in the urine invariably accompanies all types of pancreatic disease in which the activity of the gland is in the least affected. This is due to the putrefactive changes brought about in the proteids, and indican is apt to increase as the activity of the pancreas grows less, so that in cases where the pancreatic duct is obstructed, indican appears early and increases steadily to a marked degree, unless the obstruction is removed. The excessive proteid diet which is resorted to in order to satisfy hunger in certain advanced cases, adds greatly to the opportunity for putrefactive changes. With the increase in indican there is almost constantly a corresponding increase in the ethereal sulphates.

The presence of *fat* in the urine, as in the blood, is of little interest in the diagnosis of pancreatic disease, because it is present in various cachetic conditions, notably gangrene and pyemia, and in infections of the bone marrow after fractures, in chronic heart and liver disorders and even after the excessive use of fats internally or by inunction. The presence of fat acids long since noted in the urine of cases of pancreatic disease by von Jaksch is readily accounted for by Opie's discovery in the urine of a fat-splitting ferment. The fat acids may appear as the calcium and magnesium salts of the higher acids, and their crystalized appearance is said to confuse them with tyrosin, which they resemble somewhat.

The presence of oxybutyric acid in the urine, a late symptom of both pancreatic glycosuria and diabetes of other than pancreatic origin, is an indication that alkali is being removed from the body in excessive quantity, and to avoid or postpone acid intoxication must be supplied in some way. Other organic acids are occasionally present in the urine in advanced cases of glycosuria from whatever cause, but not in sufficient quantity or with sufficient regularity to be of importance. The chief one of these is diacetic acid, which rarely amounts to more than 10 per cent of the organic acid present.

The chief source of alkali used for the neutralization of the organic acids is ammonia in the formation of which both cell metabolism in the body and decomposition of proteids from the food take part. The ammonia so used is ordinarily eliminated in large part as urea, but in this acid intoxication it neutralizes the pathological acids as far as it can, and they are eliminated in combination as ammonium salts. It has recently been shown that the administration of large quantities of bicarbonate of soda in advanced states of acid intoxication has a striking power of preserving the *native alkali,* the sodium and potassium salts of the blood, which are encroached upon by the organic acids, thus relieving the condition in the same way that ammonia does.

The presence of sugar in the urine of certain persons has been definitely known since the publication of its discovery by Dobson, an English physician, over a hundred years ago. It is probable that centuries before that the fact of a peculiar sweetness to some urines was a matter of note, although the cause of this was not understood.

Since the memorable work on the pancreas of von Mehring and Minkowski, in 1890, it has been definitely proven that this organ plays a very important part in most cases of glycosuria, and it is even contended by some that as distinctly distant a condition as the glycosuria of Claude Bernhard, caused by puncture of the floor of the fourth ventricle in some way is associated with nerve changes in this organ.

Von Mehring and Minkowski found that extirpation of the pancreas in a large number of dogs was rapidly followed by all the symptoms of diabetes, the sugar elimination reaching its height in twenty-four to forty-eight hours. They further found that if a very small part of the pancreas were left behind, glycosuria did not result, and still further that if the pancreas were transplanted, and then later a large part of it removed, glycosuria did not result, unless atrophy

of the remaining part took place. A further striking phenomenon was that ligation of the pancreatic duct cutting off the supply of pancreatic juice from the intestine did not cause glycosuria, so long as there were no changes in the pancreas. This has led to the theory that the pancreas normally manufactures an internal secretion, something as the thyroid or suprarenal glands do, and that this ferment is necessary to the splitting of sugar. However this may be, the attention of the pathologists has been centered on the pancreas in all cases of diabetes and the investigations of Lagnesse, Schäfer, Diamare, Ssobolew, Opie, Wright, Herter and others, go to show a greater and greater percentage of cases of diabetes in which some lesions have been found in the islands of Langerhans, and the theory of their connection with glycosuria is strengthened greatly by the fact that no instance is on record of the islands being materially affected without there being an accompanying glycosuria.

The examination of the feces offers us both chemical and microscopical evidence of a diminution or absence of the pancreatic fluid. For clinical purposes microscopic examination is of the greater use, because certain of the changes are very easily seen and because chemical methods for fecal examinations are very complex.

The digestive power of the pancreatic juice is dependent upon at least three ferments, a fat-splitting, a starch-converting and a peptonizing ferment, known respectively as steapsin, amylopsin and trypsin, and the disturbances due to the diminution in any one or all of these ferments have definite effects upon the food taken into the stomach. The failure of the fat-splitting ferment, whose function is the emulsification of fats in which it co-operates with bile, and the splitting of neutral fats into fatty acids and glycerin, causes an increase of neutral fat in the feces. As a certain part of the fat acid is absorbed as such, recombining with the glycerin, the failure of the fat-splitting ferment deprives the system of a certain amount of one of the necessary components of food. The total amount of neutral fat eliminated may be much diminished by the fat-splitting action of bacteria in the intestinal tract.

The occurrence of a large discharge of fat with the feces, coloring it a dirty gray and giving it a slimy, glistening appearance, is not necessarily due alone to pancreatic disease. An accompanying jaundice suggests the failure of bile as the cause, but does not exclude coexistant disturbance of the pancreas. Increased fat acids do not help us to distinguish pancreatic from bile disturbances, but the presence of an excessive amount of neutral fat with diminished fat acids, points distinctly to a defective pancreatic secretion. This is an extremely significant point, and one in which accurate determinations of the fat components may be the means of determining a pancreatic lesion. It is important to remember that the presence of a normal amount of fat acid which may be produced by bacterial action, does not exclude pancreatic disease, and it is often necessary to weigh carefully the evidence from examination of the feces of an activity or failure of two of the pancreatic ferments in distinguishing disease of the pancreas from a failure of the functional activity of bile.

The failure of proteid-splitting action gives us in the feces one of the most striking results of pancreatic disease, and one of the most easily recognized, the appearance of large numbers of particles of undigested meat fibers and particles of casein. As proteid digestion is carried on in the stomach to a considerable extent, without the aid of the pancreatic ferment, it is probable before undigested proteids are present to a marked degree in the stools that the amount ingested should be much increased. When the stomach is somewhat taxed, particularly when the hunger symptoms begin, the failure of the pancreatic function is brought strongly into evidence. The impaired digestion of carbo-hydrate food, from diminution or failure of amylopsin, is probably one of the commonest causes for intestinal flatulence, and an evidence of fermentation in the feces is apparent. The resulting alcoholic intoxication or distinct poisoning from the organic acids, are causative features in the headache and drowsiness from which patients in this condition suffer. Of the glycosuria, which results from the absence of the sugar splitting ferment, I have already spoken.

The examination of fluid removed from cysts of or adjoining the pancreas is interesting, but may be of little or no value. Inasmuch as such cysts may be of immense size it seems desirable to remove the fluid by tapping in the early stages of operation, and that gives us the chance of examining it under favorable conditions. Cysts of the pancreas may not reveal a trace of any of the active ferments of that organ. Gussenbauer reports a case in which this was true. A fistula persisted and the discharged fluid was thoroughly examined, also with negative result. The fact of a pancreatic origin of the cyst was confirmed at autopsy. The presence of a starch-splitting ferment in cystic fluid has no influence in determining the origin of the fluid, because the ferment is present in various forms of cystic tumors found in the abdomen. Any or all the ferments may be present also in the pseudo-cysts or para-pancreatic cysts which arise outside but adjoining the pancreas from disease or injury to it.

Hydatids of the pancreas are practically unknown and the contents of a hydatid cyst are rarely hemorrhagic, whereas pancreatic cysts most always contain a brownish pigment from

altered blood coming from the hemorrhages so frequently associated with the pathologic conditions of the pancreas.

RÉSUMÉ.

Glycosuria as a symptom of pancreatic disease seems to be definitely associated with pathologic conditions in the islands of Langerhans, and is a development in many cases of the *later* periods of the disease. Processes involving the islands of Langerhans primarily do occur, and thus far no case has been reported in which such a process is not accompanied by glycosuria, although glycosuria *does* occur in cases in which the islands have been found unaffected at post mortem.

Steatorrhea is a symptom both of failure of the bile and of the pancreatic fluid. A failure of the bile to enter the intestine has a distinct influence in lessening the flow of pancreatic fluid on account of the stimulation which bile is to the activity of the pancreas. Further occlusions of the lower end of the common duct shut off the pancreatic fluid, and if bile is forced into the pancreatic duct in consequence, acute inflammatory disturbances may result in the gland. The steatorrhea of primary pancreatic disease in which there is a diminution or absence of pancreatic secretion is marked by an excessive increase in the neutral fats, reaching even 60 per cent of the total excretion, instead of the normal, of about 10 per cent to 15 per cent, and further by a striking diminution of fatty acids. With the steatorrhea is microscopic evidence of a failure of proteid digestion, shown by the finding of muscle fibers and casein coagula.

Fermentative and excessive putrefactive changes in the feces are evident to the eye and nose.

Indican is present in increased amount in the urine, as are also the ethereal sulphates.

The methylene blue test of Williamson may be used to determine a hyperglycemia in a suspected case of diabetic coma, when means of obtaining urine are not at hand. Bremer's test is less useful in the same condition.

Lipuria and lipemia are interesting, but not pathognomonic symptoms.

The presence of a fat-splitting ferment in the urine might be of extreme value in fixing a pancreatic connection to a glycosuria or to an acute disturbance in the epigastrium.

A CASE OF PANCREATIC CYST.*

By ELMER E. KELLY, M. D.

THE PANCREAS is an organ so deeply hidden away in the abdominal cavity and so hedged about with delicate anatomical structures that until recent years it has been considered a *terra incognito* by the abdominal surgeon. But with the advent of aseptic surgery the emboldened surgeon has explored every tissue and organ until no unknown quarter remains.

Even yet, however, there are organs and structures that have so rarely been removed or operated upon that every case deserves to be reported that the general store of knowledge may be increased and the statistical value of the various operations obtained. For this reason I have thought it worth while to make a record of the following case of pancreatic cyst:

G. W. C., aged 41, appeared at my office November 14, 1902, and from him I gleaned the following history:

Ten years ago the patient was suddenly attacked by excruciating pain in the epigastric region, accompanied by vomiting, after having eaten heartily of pork sausages. His physician thought the probable cause of the disturbance was due to the meat he had eaten.

The attack lasted thirty-six hours and by other physicians was diagnosed to be due to gall stones. There was no icterus and no lack of bile noticed in the patient's stools. An interval of six months passed before another attack, but three months later a third attack occurred and followed pretty much the same course as the previous ones, except that the patient lost flesh rapidly and became greatly debilitated. Four years after the initial attack he came to San Francisco and was treated for kidney disease, with marked improvement. Six months later he suffered a severe and more prolonged attack of pain, noticeable especially after eating. For the next twelve or fourteen months he was able to attend to his business, though he was not at all well. Then followed a series of severe though short attacks of pain which were only relieved by the use of morphine. At this time the malady was diagnosed as inflammation of the bowels and long shreds resembling mucous membrane were passed with the stools. Various plans of treatment were followed without material benefit. In 1898 he had a very severe attack lasting eleven days, during which, for the first time, he became deeply jaundiced, which continued for seven days. A large number of gall stones were passed in the stools, after which he was relieved of his pains. For one year he remained free from gastric pain and irritation.

Upon the 17th of August, 1902, he was again attacked by his old enemy, the jaundice reappeared, and after a few days of intense suffering, more gall stones were passed per rectum. The epigastric pains became more intense, radiating over the entire abdomen. Again the stools showed the presence of long shreds resembling mucous membrane, and his physician assured him that he was passing portions of the mucous lining of his bowels. Four weeks after the beginning of the attack he noticed his abdomen increasing in size, especially noticeable in the upper portion, in the epigastric region. This enlargement was accompanied by dyspepsia and inability to lie down flat in the bed. Pain invariably followed eating or drinking, and emaciation became quite marked, his weight being reduced from 210 to 138 pounds. Patient did not notice that one kind of food caused

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